REMARKS

The non-final Office Action dated March 31, 2003 has been received and reviewed. Claims 1, 3, 4, 6-12, 14-18, 21 are pending in the application. Claims 2, 5, 13, 19 and 20 were previously cancelled. By way of the present communication, claims 1, 18 and 21 are amended, and new claims 22-36 are added. Claims 1, 3, 4, 6-12, 14-18, and 21 stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Reconsideration is respectfully requested.

1. Specification:

The Cross-reference to related applications was objected to for failing to indicate that the international application from which this application claims priority was published in English. The specification has been amended as suggested by the Examiner.

2. Claim Rejections Under 35 U.S.C. § 112, 2nd ¶:

Claims 1, 3, 4, 6-12, 14-18 and 21 have been rejected under 35 U.S.C. § 112, second paragraph, for assertedly failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention.

Specifically, claim 18 was rejected for lacking antecedent basis due to reference to claim 2, which was previously cancelled. Claim 18 has been amended to correct this inadvertent error by changing its dependency to claim 21. Accordingly, the rejection is believed to have been overcome and withdrawal thereof is respectfully requested.

Additionally, claims 1, 3, 4, 6-12, 14-18 and 21 were rejected as assertedly being incomplete because essential steps were omitted, such omissions amounting to a gap between the steps. Claims 1 and 21 have been amended as suggested by the Examiner by adding the following language, "to a mammal with inflammatory bowel disease." Accordingly, this rejection is believed to have been overcome and withdrawal thereof is respectfully requested.

3. Claim Rejections Under 35 U.S.C. § 112, 1st ¶:

Claim 21 has been rejected under 35 U.S.C. § 112, first paragraph for assertedly not reasonably enabling one to prevent inflammatory bowel disease ("IBD") in a mammal using the claimed method. Specifically, it was asserted that ulcerative colitis and Crohn's Disease ("CD") have a relatively well characterized etiology, but the etiology of IBD is not well characterized. Further, it was thought that it would not be apparent to one skilled in the art how to reasonably extrapolate from a mouse to "any subject" without an undue amount of experimentation. Applicants respectfully request reconsideration.

With respect to claim 21, some subjects have a known genetic predisposition (*i.e.*, possess a specific genotype) for developing IBD later in their life. The specification explicitly supports prevention of inflammation of the bowel as disclosed in claim 21.

IBD (*i.e.*, ulcerative colitis and CD, the two predominant IBD diseases) is a complex intestinal disorder with immunologic, environmental and genetic components. There is ample evidence that IBD is in part the result of genetic predisposition. See, Duerr, RH, *Gastroenterol Clin North Am*, (1):63-76 (2002). Thus, based on a genetic profile, subjects that have a substantially increased risk of developing IBD can be identified. Subjects can easily be tested for currently known genetic markers for IBD and for other markers identified in the future. One such currently identified marker is the polymorphism of the CARD15/NOD2 gene. Ogurea, *et al.*, *Nature* 411(6837):599-606 (2001), and Hugot, *et al.*, *Nature* 411(6837):599-603 (2001). These results, published in one of the most highly respected, peer-reviewed scientific journals, clearly links genetic variation to onset of disease. Specifically, the mutations in the CARD15/NOD2 gene appear to be related to evolution towards pronounced disease. Hampe, *et al.*, *Lancet* 359(9318):1661-1665 (2002). It has been postulated that "...identification of additional disease-genes in inflammatory bowel disease will further promote development of paradigms for early and preventive treatment . . . In this respect, genetic variables will be especially useful, since genetics-based classification is more stable than exclusive use of clinical features (which depend themselves on disease duration and activity)." See, Hampe, *et al.* It is now generally accepted among experts in the field that prognosis of the development of IBD can be made and that there is a clear therapeutic window for preventive intervention.

In a similar way, IL-10 deficient mice, although born with a healthy gut, are predisposed to developing intestinal inflammation. Kuhn *et al*, *Cell* 75(2):263-274 (1993). This animal model is currently one of the most accepted simulations for IBD. The specification reveals applicants' elegant demonstration of the genetic predisposition for IBD. The data disclosed in the specification clearly shows that the administration of IL-10 secreting *Lactococcus* can prevent the onset of intestinal inflammation in mice. Thus, it is obvious to one skilled in the art that such treatment can also result in the prevention of IBD in people with genetic predisposition for the development of IBD.

The principle of preventive intervention is not new. Caprilli, *et al.*, describe a treatment to prevent recurrent CD after surgery. *Aliment Pharmacol Ther* 17(4):517-523 (2003). Appendectomy can prevent CD and ulcerative colitis. Radford-Smith, *et al.*, *Gut* 51(6):808-813 (2002). Demonstration that prophylactic administration of FGF-20 can significantly reduce the severity and extent of mucosal damage shows that this principle can be expanded to molecular medicine. Jeffers, *et al.*, *Gastroenterology* 123(4):1151-1162 (2002).

Applicants have claimed that the subject being treated is a mammal. As discussed at the interview (October 8, 2002), the particular mouse model described in the examples is well accepted in the relevant art, and should provide adequate support for the breadth of the claim. In support of this contention, an article authored by the inventors of the present invention and published in the renowned journal *Science* (*Science* 2000: 1352-1355) was previously submitted with the Office Action Response filed April 17, 2002. It is stated in the abstract thereof that "[t]his approach may lead to better methods for cost-effective and long-term management of IBD *in humans*" (emphasis added). A statement such as this undoubtedly would not be published in a renowned peer-reviewed journal like *Science* if the extrapolation from mice to other mammals was unacceptable to those of skill in the art.

Further, Papadakis *et al.*, *Annu. Rev. Med.*, vol. 51, pp. 289–298, 289 (2000) ("Papadakis") states that the development of animal models of intestinal inflammation to approximate human IBD has expanded our understanding of the pathogenesis of ulcerative colitis and CD and has opened new avenues for the development and testing of novel therapeutics. *Id.* at 289. Papadakis also states that more than twenty animal models of intestinal inflammation

have been described and provided the opportunity to study the pathology of mucosal inflammation as well as to "test several therapeutic interventions for potential treatment of human disease." *Id.* at 292. Thus, in the context of IBD, the murine model is widely accepted by those of ordinary skill in the art as a model for the treatment of humans and other mammals. Several other noted scientists have come forward to state that results in the mouse model can be extrapolated to therapeutic application other mammals. Shanahan, F. *Science* 289, 1311-1312 (2000), and Gordon, D. *Gastroenterology* 119, 1187-1188 (2000). Furthermore, Harvard Medical School Professor Richard S. Blumberg, Chair of the Crohn's and Colitis Foundation of America, has invited the applicants to begin clinical trials based on the data applicants published in the journal *Science*. Illustrating the scientific community's readiness to apply these model studies to other mammals, the first clinical trials, using the disclosures contained herein, are being conducted with Professor Sander van Deventer at the Academisch Medisch Centrum in Amsterdam, The Netherlands. Preliminary results are reportedly very encouraging.

It is respectfully submitted that inflammatory bowel diseases, whether ulcerative colitis or CD, are characterized by chronic inflammation of the intestinal mucosa. *See*, the Papadakis reference at page 289. Such mucosal inflammation may occur in various portions of the intestine, for example, the caecum, ascending colon, descending colon, transverse colon and the like. A particular mammal may have inflammation in one or more of these intestinal portions but not in others at the time the disease is diagnosed and treatment begins. The results set forth in the specification illustrate that administration of the medicament may both reduce inflammation in those areas of the intestine already affected *and* prevent inflammation in other portions of the intestine, *i.e.*, prevent spread of the inflammation. Thus, it is respectfully submitted that reduction and prevention of inflammation may be affected based on the disclosed studies using the well-established mouse IL10-/- model.

In the non-final office action of March 31, 2003, it was alleged that "[t]he specification provides sufficient guidance for one skilled in the art to practice a method of preventing the onset of colitis in a IL10-/- mouse using cytokine- or cytokine antagonist producing genetically modified, non-invasive Gram-positive bacteria." Claim 21 concerns prevention of IBD in mammals based on similar tests performed in the same mouse model. The specification

explicitly illustrates that prevention was observed in the same mouse model. Dr. Lothar Steidler's 37 C.F.R. 1.132 earlier declaration specifically points out that these prevention studies were published in a highly respected, peer-reviewed journal. *Science* 289:1352-1355 (2000).

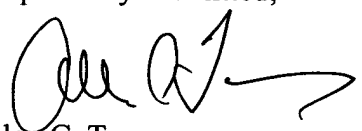
In view of the foregoing, applicants request that the rejections be withdrawn.

Applicants have added claims 22-36 for consideration. It is respectfully submitted these claims are in condition for acceptance. Applicants respectfully submit that introduction of these new claims does not constitute addition of new matter to the application.

CONCLUSION

In view of the present amendments and remarks, the remaining claims are believed to be in condition for allowance and an early notice thereof respectfully is solicited. Should the Office determine that additional issues remain which might be resolved by a telephone conference, the Office respectfully is invited to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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